Supplementary Material

Supplementary Material 3: Additional Results

S3.1 List of included and excluded studies (with reasons)

S3.2 Risk of Bias assessment

S3.3 Additional figures and forest plots

S3.4 Results from Thigpen 2012 (by gender)

S3.5 Adherence

S3.6 Change in sexual behaviour/STI rates

O Murchu E, *et al. BMJ Open* 2022; 12:e048478. doi: 10.1136/bmjopen-2020-048478

Supplementary Material

S3.1

List of studies included in review

1. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. New England journal of medicine [Internet]. 2012; 367(5):[399-410 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/266/CN-00840266/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3770474/pdf/nihms493581.pdf.

2. Baeten JM, Heffron R, Kidoguchi L, Mugo NR, Katabira E, Bukusi EA, et al. Integrated Delivery of Antiretroviral Treatment and Pre-exposure Prophylaxis to HIV-1–serodiscordant Couples: A Prospective Implementation Study in Kenya and Uganda. PLOS Medicine. 2016;13(8):e1002099.

3. Bekker LG, Roux S, Sebastien E, Yola N, Amico KR, Hughes JP, et al. Daily and non-daily pre-exposure prophylaxis in African women (HPTN 067/ADAPT Cape Town Trial): a randomised, open-label, phase 2 trial. The lancet HIV. 2018;5(2):e68-e78.

4. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet (London, England). 2013;381(9883):2083-90.

5. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. New England journal of medicine [Internet]. 2010; 363(27):[2587-99 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/306/CN-00771306/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3079639/pdf/nihms264954.pdf.

6. Grohskopf LA, Chillag KL, Gvetadze R, Liu AY, Thompson M, Mayer KH, et al. Randomized trial of clinical safety of daily oral tenofovir disoproxil fumarate among HIV-uninfected men who have sex with men in the United States. Journal of acquired immune deficiency syndromes (1999). 2013;64(1):79-86.

7. Hosek SG, Siberry G, Bell M, Lally M, Kapogiannis B, Green K, et al. The acceptability and feasibility of an HIV preexposure prophylaxis (PrEP) trial with young men who have sex with men. Journal of acquired immune deficiency syndromes (1999). 2013;62(4):447-56.

8. Kibengo FM, Ruzagira E, Katende D, Bwanika AN, Bahemuka U, Haberer JE, et al. Safety,

adherence and acceptability of intermittent tenofovir/emtricitabine as HIV pre-exposure prophylaxis (PrEP) among HIV-uninfected Ugandan volunteers living in HIV-serodiscordant relationships: a randomized, clinical trial. PLoS One. 2013;8(9):e74314.

9. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. The New England journal of medicine. 2015;372(6):509-18.

10. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet (London, England). 2016;387(10013):53-60.

11. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. The New England journal of medicine. 2015;373(23):2237-46.

12. Mutua G, Sanders E, Mugo P, Anzala O, Haberer JE, Bangsberg D, et al. Safety and adherence to intermittent pre-exposure prophylaxis (PrEP) for HIV-1 in African men who have sex with men and female sex workers. Plos one [Internet]. 2012; 7(4):[e33103 p.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/614/CN-00848614/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3325227/pdf/pone.0033103.pdf.

13. Peterson L, Taylor D, Roddy R, Belai G, Phillips P, Nanda K, et al. Tenofovir Disoproxil Fumarate for Prevention of HIV Infection in Women: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial. PLoS Clinical Trials. 2007;2(5):e27.

14. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. New England journal of medicine [Internet]. 2012; 367(5):[423-34 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/265/CN-00840265/frame.html.

15. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. The New England journal of medicine. 2012;367(5):411-22.

Supplementary Material

List of studies excluded from review

1. Agot K, Taylor D, Corneli AL, Wang M, Ambia J, Kashuba AD, et al. Accuracy of Self-Report and Pill-Count Measures of Adherence in the FEM-PrEP Clinical Trial: Implications for Future HIV-Prevention Trials. AIDS and behavior. 2015;19(5):743-51. [reason: secondary analysis of FEM-PrEP]

2. Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama JR, Guanira JV, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Science translational medicine. 2012;4(151):151ra25. [reason: secondary analysis of iPrEX]

3. Baeten JM, Donnell D, Mugo NR, Ndase P, Thomas KK, Campbell JD, et al. Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial. The lancet Infectious diseases [Internet]. 2014; 14(11):[1055-64 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/639/CN-01053639/frame.html https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4252589/pdf/nihms635147.pdf. [reason: duplicate]

4. Buchbinder SP, Glidden DV, Liu AY, McMahan V, Guanira JV, Mayer KH, et al. HIV pre-exposure prophylaxis in men who have sex with men and transgender women: a secondary analysis of a phase 3 randomised controlled efficacy trial. The Lancet Infectious diseases. 2014;14(6):468-75. [reason: secondary analysis of iPrEX]

5. Buchbinder SP, Liu AY. CROI 2014: New tools to track the epidemic and prevent HIV infections. Topics in Antiviral Medicine. 2014;22(2):579-93. [reason: review; not a RCT]

6. Campbell JD, Herbst JH, Koppenhaver RT, Smith DK. Antiretroviral prophylaxis for sexual and injection drug use acquisition of HIV. American Journal of Preventive Medicine. 2013;44(1 SUPPL. 2):S63-S9. [reason: review, not a RCT]

7. Celum C, Baeten JM. Antiretroviral-based HIV-1 prevention: Antiretroviral treatment and pre-exposure prophylaxis. Antiviral Therapy. 2012;17(8):1483-93. [reason: review/not a RCT]

8. Corneli AL, Deese J, Wang M, Taylor D, Ahmed K, Agot K, et al. FEM-PrEP: adherence patterns and factors associated with adherence to a daily oral study product for pre-exposure prophylaxis. Journal of acquired immune deficiency syndromes (1999). 2014;66(3):324-31. [reason: secondary analysis of FEM-PrEP]

9. Corneli AL, McKenna K, Headley J, Ahmed K, Odhiambo J, Skhosana J, et al. A descriptive analysis of perceptions of HIV risk and worry about acquiring HIV among FEM-PrEP

participants who seroconverted in Bondo, Kenya, and Pretoria, South Africa. Journal of the International AIDS Society. 2014;17(3). [reason: secondary analysis of FEM-PrEP]

10. Deutsch MB, Glidden DV, Sevelius J, Keatley J, McMahan V, Guanira J, et al. HIV pre-exposure prophylaxis in transgender women: a subgroup analysis of the iPrEx trial. The lancet HIV. 2015;2(12):e512-9. [reason: secondary analysis of iPrEX]

11. Dolling DI, Desai M, McOwan A, Gilson R, Clarke A, Fisher M, et al. An analysis of baseline data from the PROUD study: An open-label randomised trial of pre-exposure prophylaxis. Trials. 2016;17(1). [reason: secondary analysis of PROUD]

12. Dunn DT, Glidden DV. Statistical issues in trials of preexposure prophylaxis. Current Opinion in HIV and AIDS. 2016;11(1):116-21. [reason: review/not a RCT]

13. Elbirt D, Mahlab-Guri K, Bezalel-Rosenberg S, Asher I, Sthoeger Z. Pre-exposure prophylaxis as a method for prevention of human immunodeficiency virus infection. Israel Medical Association Journal. 2016;18(5):294-8. [reason: review, not a RCT]

14. Fidler S, Bock P. Prophylactic antiretroviral HIV therapy prevents infection in heterosexual men and women. Evidence-Based Medicine. 2013;18(5):184-5. [Reason: not a RCT, review of Baeten et al.]

15. Gilmore HJ, Liu A, Koester KA, Amico KR, McMahan V, Goicochea P, et al. Participant experiences and facilitators and barriers to pill use among men who have sex with men in the iPrEx pre-exposure prophylaxis trial in San Francisco. AIDS patient care and stds [Internet]. 2013; 27(10):[560-6 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/551/CN-00962551/frame.html. [reason: secondary analysis of iPrEX]

16. Grangeiro A, Couto MT, Peres MF, Luiz O, Zucchi EM, de Castilho EA, et al. Pre-exposure and postexposure prophylaxes and the combination HIV prevention methods (The Combine! Study): protocol for a pragmatic clinical trial at public healthcare clinics in Brazil. BMJ open. 2015;5(8):e009021. [reason: protocol]

17. Grant RM, Liegler T, Defechereux P, Kashuba AD, Taylor D, Abdel-Mohsen M, et al. Drug resistance and plasma viral RNA level after ineffective use of oral pre-exposure prophylaxis in women. AIDS (London, England). 2015;29(3):331-7. [reason: not an efficacy RCT; further analysis of FEM-PrEP]

18. Gray RH, Wawer MJ. Infection in 2012: Mixed results of pre-exposure prophylaxis for HIV prevention. Nature Reviews Urology. 2013;10(2):74-5. [reason: review]

19. Gulick RM, Wilkin TJ, Chen YQ, Landovitz RJ, Amico KR, Young AM, et al. Phase 2 Study of the Safety and Tolerability of Maraviroc-Containing Regimens to Prevent HIV

Infection in Men Who Have Sex With Men (HPTN 069/ACTG A5305). The Journal of infectious diseases. 2017;215(2):238-46. [reason: different intervention (maraviroc)]

20. Gulick RM, Wilkin TJ, Chen YQ, Landovitz RJ, Amico KR, Young AM, et al. Safety and Tolerability of Maraviroc-Containing Regimens to Prevent HIV Infection in Women: A Phase 2 Randomized Trial. Annals of internal medicine. 2017;167(6):384-93. [reason: different intervention (maraviroc)]

21. Gust DA, Soud F, Hardnett FP, Malotte CK, Rose C, Kebaabetswe P, et al. Evaluation of Sexual Risk Behavior Among Study Participants in the TENOFOVIR2 PrEP Study Among Heterosexual Adults in Botswana. Journal of acquired immune deficiency syndromes (1999). 2016;73(5):556-63. [reason: secondary analysis of TD2 trial]

22. Haberer JE, Baeten JM, Campbell J, Wangisi J, Katabira E, Ronald A, et al. Adherence to Antiretroviral Prophylaxis for HIV Prevention: A Substudy Cohort within a Clinical Trial of serodiscordant Couples in East Africa. PLoS Medicine. 2013;10(9). [reason: secondary analysis of Partners PrEP]

23. Hanscom B, Janes HE, Guarino PD, Huang Y, Brown ER, Chen YQ, et al. Brief report: Preventing HIV-1 infection in women using oral preexposure prophylaxis: A meta-analysis of current evidence. Journal of Acquired Immune Deficiency Syndromes. 2016;73(5):606-8. [reason: meta-analysis of RCTs]

24. Jiang J, Yang X, Ye L, Zhou B, Ning C, Huang J, et al. Pre-exposure prophylaxis for the prevention of HIV infection in high risk populations: A meta-analysis of randomized controlled trials. PLoS ONE. 2014;9(2). [reason: meta-analysis of existing RCTs]

25. K RA, McMahan V, Goicochea P, Vargas L, Marcus JL, Grant RM, et al. Supporting study product use and accuracy in self-report in the iPrEx study: next step counseling and neutral assessment. AIDS and behavior. 2012;16(5):1243-59. [reason: secondary analysis of iPrEX]

26. Koester KA, Liu A, Eden C, Amico KR, McMahan V, Goicochea P, et al. Acceptability of drug detection monitoring among participants in an open-label pre-exposure prophylaxis study. AIDS Care - Psychological and Socio-Medical Aspects of AIDS/HIV. 2015;27(10):1199-204. [reason: observational study on subset of iPrEX OLE study]

27. Koss CA, Bacchetti P, Hillier SL, Livant E, Horng H, Mgodi N, et al. Differences in Cumulative Exposure and Adherence to Tenofovir in the VOICE, iPrEx OLE, and PrEP Demo Studies as Determined via Hair Concentrations. AIDS Research and Human Retroviruses. 2017;33(8):778-83. [reason: secondary analysis of 3 studies]

28. Lehman DA, Baeten JM, McCoy CO, Weis JF, Peterson D, Mbara G, et al. Risk of drug resistance among persons acquiring HIV within a randomized clinical trial of single-or

dual-agent preexposure prophylaxis. Journal of Infectious Diseases. 2015;211(8):1211-8. [reason: secondary analysis of Partners PrEP study]

29. Liu A, Glidden DV, Anderson PL, Amico KR, McMahan V, Mehrotra M, et al. Patterns and correlates of PrEP drug detection among MSM and transgender women in the global iPrEx study. Journal of Acquired Immune Deficiency Syndromes. 2014;67(5):528-37. [reason: secondary analysis of iPrEX]

30. Liu AY, Vittinghoff E, Chillag K, Mayer K, Thompson M, Grohskopf L, et al. Sexual risk behavior among HIV-uninfected men who have sex with men participating in a tenofovir preexposure prophylaxis randomized trial in the United States. Journal of acquired immune deficiency syndromes (1999). 2013;64(1):87-94. [reason: secondary analysis of US CDC Safety Study]

31. Lorente N, Fugon L, Carrieri MP, Andreo C, Le Gall JM, Cook E, et al. Acceptability of an on-demand pre-exposure HIV prophylaxis trial among men who have sex with men living in France. AIDS Care - Psychological and Socio-Medical Aspects of AIDS/HIV. 2012;24(4):468-77. [reason: acceptability study prior to RCT]

32. Markowitz M, Frank I, Grant RM, Mayer KH, Elion R, Goldstein D, et al. Safety and tolerability of long-acting cabotegravir injections in HIV-uninfected men (ECLAIR): a multicentre, double-blind, randomised, placebo-controlled, phase 2a trial. The lancet HIV. 2017;4(8):e331-e40. [reason: intervention different (cabotegravir)]

33. Martin M, Vanichseni S, Suntharasamai P, Sangkum U, Chuachoowong R, Mock PA, et al. Enrollment characteristics and risk behaviors of injection drug users participating in the Bangkok Tenofovir Study, Thailand. PLoS One. 2011;6(9):e25127. [reason: secondary analysis of Bangkok tenofovir study enrolment characteristics]

34. Martin M, Vanichseni S, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Risk behaviors and risk factors for HIV infection among participants in the Bangkok tenofovir study, an HIV pre-exposure prophylaxis trial among people who inject drugs. PLoS One. 2014;9(3):e92809. [reason: secondary analysis of Bangkok tenofovir study enrolment characteristics]

35. McCormack SM, Noseda V, Molina JM. PrEP in Europe - Expectations, opportunities and barriers. Journal of the International AIDS Society. 2016;19. [reason: not a RCT; review article]

36. Mehrotra ML, Westreich D, McMahan VM, Glymour MM, Geng E, Grant RM, et al. Baseline Characteristics Explain Differences in Effectiveness of Randomization to Daily Oral TDF/FTC PrEP Between Transgender Women and Cisgender Men Who Have Sex With Men in the iPrEx Trial. Journal of acquired immune deficiency syndromes (1999).

2019;81(3):e94-e8. Epub 2019/06/14. doi: 10.1097/qai.0000000000002037. [reason: secondary analysis iPrEX]

37. Mills A, Workowski K, Campbell T, Benson P, Crofoot G, Salazar L, et al. Renal outcomes for participants taking F/TAF vs. F/TDF for HIV PrEP in the DISCOVER trial. Open Forum Infectious Diseases. 2019;6:S64. doi: 10.1093/ofid/ofz359.139. [reason: review; no efficacy data]

38. Miltz AR, Lampe FC, Bacchus LJ, McCormack S, Dunn D, White E, et al. Intimate partner violence, depression, and sexual behaviour among gay, bisexual and other men who have sex with men in the PROUD trial. BMC public health. 2019;19(1):431. Epub 2019/04/27. doi: 10.1186/s12889-019-6757-6.. [reason: secondary analysis PROUD]

39. Mugwanya KK, Donnell D, Celum C, Thomas KK, Ndase P, Mugo N, et al. Sexual behaviour of heterosexual men and women receiving antiretroviral pre-exposure prophylaxis for HIV prevention: a longitudinal analysis. The lancet Infectious diseases [Internet]. 2013; 13(12):[1021-8 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/297/CN-00915297/frame.html. [reason: longitudinal analysis of Partners PrEP]

40. Mujugira A, Baeten JM, Donnell D, Ndase P, Mugo NR, Barnes L, et al. Characteristics of HIV-1 serodiscordant couples enrolled in a clinical trial of antiretroviral pre-exposure prophylaxis for HIV-1 prevention. Plos one [Internet]. 2011; 6(10):[e25828 p.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/232/CN-00805232/frame.html. [reason: secondary analysis Partners PrEP]

41. Murnane PM, Brown ER, Donnell D, Coley RY, Mugo N, Mujugira A, et al. Estimating Efficacy in a Randomized Trial With Product Nonadherence: Application of Multiple Methods to a Trial of Preexposure Prophylaxis for HIV Prevention. American Journal of Epidemiology. 2015;182(10):848-56. [reason: secondary analysis Partners PrEP]

42. Murnane PM, Celum C, Mugo N, Campbell JD, Donnell D, Bukusi E, et al. Efficacy of preexposure prophylaxis for HIV-1 prevention among high-risk heterosexuals: subgroup analyses from a randomized trial. AIDS (london, england) [Internet]. 2013; 27(13):[2155-60 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/174/CN-01000174/frame.html. [reason: secondary analysis Partners PrEP]

43. Ndase P, Celum C, Campbell J, Bukusi E, Kiarie J, Katabira E, et al. Successful discontinuation of the placebo arm and provision of an effective HIV prevention product after a positive interim efficacy result: the partners PrEP study experience. Journal of acquired immune deficiency syndromes (1999) [Internet]. 2014; 66(2):[206-12 pp.]. Available from: http://cochranelibrary-

wiley.com/o/cochrane/clcentral/articles/717/CN-00992717/frame.html. [reason: review of Partners PrEP]

44. O'Halloran C, Rice B, White E, Desai M, D TD, McCormack S, et al. Chemsex is not a barrier to self-reported daily PrEP adherence among PROUD study participants. International Journal of Drug Policy. 2019;74:246-54. doi: 10.1016/j.drugpo.2019.10.007 [reason: secondary analysis PROUD]

45. Page K, Tsui J, Maher L, Choopanya K, Vanichseni S, Philip Mock M, et al. Biomedical HIV prevention including pre-exposure prophylaxis and opiate agonist therapy for women who inject drugs: State of research and future directions. Journal of Acquired Immune Deficiency Syndromes. 2015;69:S169-S75. [reason: review; not a RCT]

46. Post F, Spinner C, Coll P, Hawkins T, Anderson J, Zhong L, et al. DISCOVER in Europe: A sub-analysis of the phase 3 randomized, controlled trial of daily emtricitabine/tenofovir alafenamide (F/TAF) or emtricitabine/tenofovir disoproxil fumarate (F/TDF) for HIV pre-exposure prophylaxis (PrEP). HIV Medicine. 2019;20:243-4. doi: 10.1111/hiv.12815. [reason: abstract only/no full text available]

47. Roux P, Fressard L, Suzan-Monti M, Chas J, Sagaon-Teyssier L, Capitant C, et al. Is on-Demand HIV Pre-exposure Prophylaxis a Suitable Tool for Men Who Have Sex With Men Who Practice Chemsex? Results From a Substudy of the ANRS-IPERGAY Trial. Journal of acquired immune deficiency syndromes (1999). 2018;79(2):e69-e75. Epub 2018/09/14. doi: 10.1097/qai.0000000000001781. [reason: secondary analysis IPERGAY]

48. Ruane PJ, Clarke A, Post FA, Schembri G, Jessen H, Trottier B, et al. Phase 3 randomized, controlled DISCOVER study of daily emtricitabine/tenofovir alafenamide (F/TAF) or emtricitabine/tenofovir disoproxil fumarate (F/TDF) for HIV pre-exposure prophylaxis (PrEP): Week 96 results. HIV Medicine. 2019;20:95-6. doi: 10.1111/hiv.12815. [reason: abstract only/no full text available]

49. Sacks HS. Preexposure tenofovir-emtricitabine reduced HIV infection in men who have unprotected anal sex with men. Annals of Internal Medicine. 2016;164(2):JC3. [reason: review of PROUD]

50. Spinner CD, Brunetta J, Shalit P, Prins M, Cespedes M, Brainard D, et al. DISCOVER study for HIV pre-exposure prophylaxis (PrEP): F/TAF has a more rapid onset and longer sustained duration of HIV protection compared with F/TDF. Journal of the International AIDS Society. 2019;22. doi: 10.1002/jia2.25327. [reason: abstract only/no full text available]

51. Thomson KA, Baeten JM, Mugo NR, Bekker LG, Celum CL, Heffron R. Tenofovir-based oral preexposure prophylaxis prevents HIV infection among women. Current Opinion in HIV and AIDS. 2016;11(1):18-26. [reason: review; not a RCT]

52. Velloza J, Bacchetti P, Hendrix CW, Murnane P, Hughes JP, Li M, et al. Short- and Long-Term Pharmacologic Measures of HIV Pre-exposure Prophylaxis Use Among High-Risk Men Who Have Sex With Men in HPTN 067/ADAPT. Journal of acquired immune deficiency syndromes (1999). 2019;82(2):149-58. Epub 2019/07/25. doi: 10.1097/qai.0000000000002128. [reason: secondary analysis HPTN 067/ADAPT]

53. Vermund SH. Safety and tolerability of tenofovir for preexposure prophylaxis among men who have sex with men. Journal of Acquired Immune Deficiency Syndromes. 2013;64(1):3-6. [reason: review; not a RCT]

54. White E, Dunn DT, Desai M, Gafos M, Kirwan P, Sullivan AK, et al. Predictive factors for HIV infection among men who have sex with men and who are seeking PrEP: a secondary analysis of the PROUD trial. Sexually transmitted infections. 2019;95(6):449-54. Epub 2019/03/29. doi: 10.1136/sextrans-2018-053808.. [reason: secondary analysis PROUD]

55. Wohl D, Ruane P, Hosek S, Creticos C, Morris S, Phoenix J, et al. Bone safety outcomes with F/TAF vs. F/TDF for PrEP in the DISCOVER trial. Open Forum Infectious Diseases. 2019;6:S464. doi: 10.1093/ofid/ofz360.1151. [reason: review; no efficacy data]

56. Yacoub R, Nadkarni GN, Weikum D, Konstantinidis I, Boueilh A, Grant RM, et al. Elevations in serum creatinine with tenofovir-based HIV pre-exposure prophylaxis: A meta-analysis of randomized placebo-controlled trials. Journal of Acquired Immune Deficiency Syndromes. 2016;71(4):e115-e8. [reason: meta-analysis of RCTs]

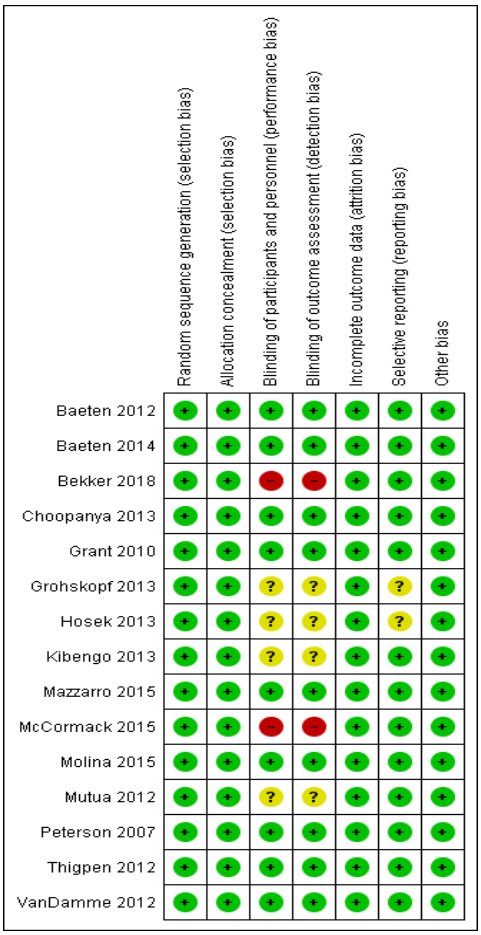
Supplementary Material

S3.2

Risk of Bias assessment

Two studies were open-label trials and, as such, blinding of participants or investigators was not possible. A further three studies were placebo-controlled trials that additionally investigated alternate dosing schedules; while participants and investigators were blinded to drug assignment, they could not be blinded to regimen assignment. One study contained a 'no pill' arm that could not be blinded in addition to a placebo arm. Two studies had unclear risk for reporting bias due to the fact that study protocols were not available. Figure S1 represents the review authors' judgements about each risk of bias item for each included study.

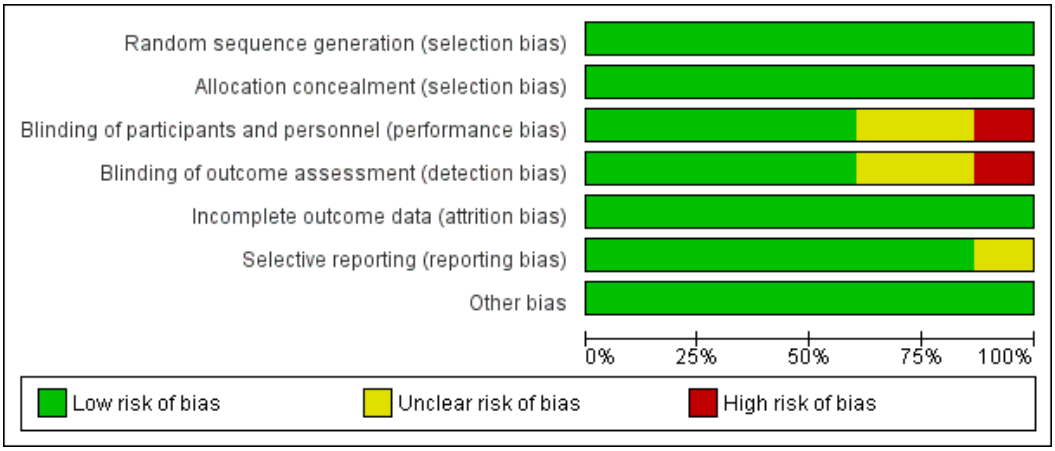
Figure S1. Risk of bias summary



Supplementary Material

Figure S2 represents the review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure S2. Risk of bias graph



Supplementary Material

S3.3 Additional figures and forest plots

Efficacy

Figure S3. Meta-analysis: HIV acquisition, all trials (PrEP versus placebo or no drug)

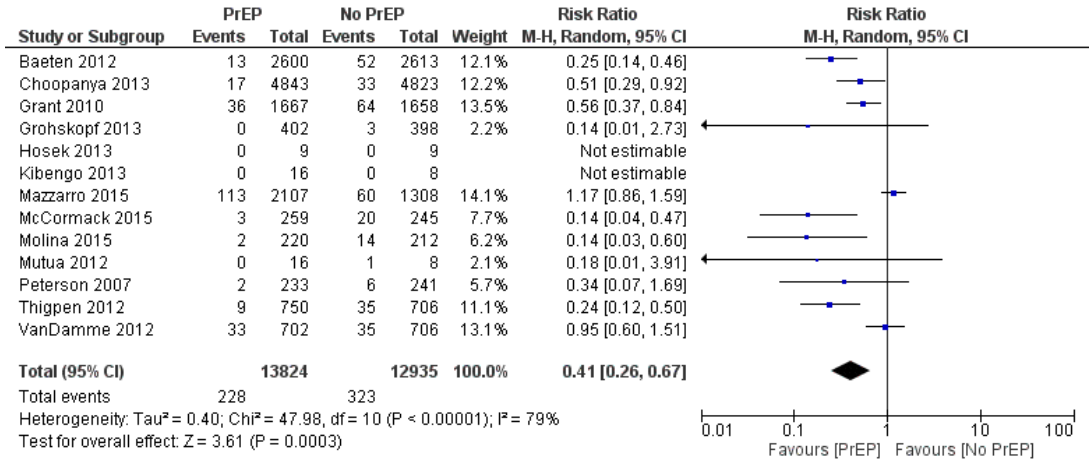


Figure S4. Meta-analysis: HIV acquisition in heterosexual participants, PrEP versus placebo, all trials

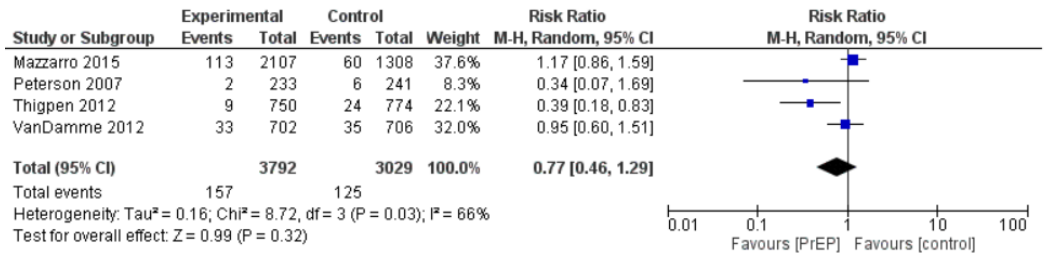
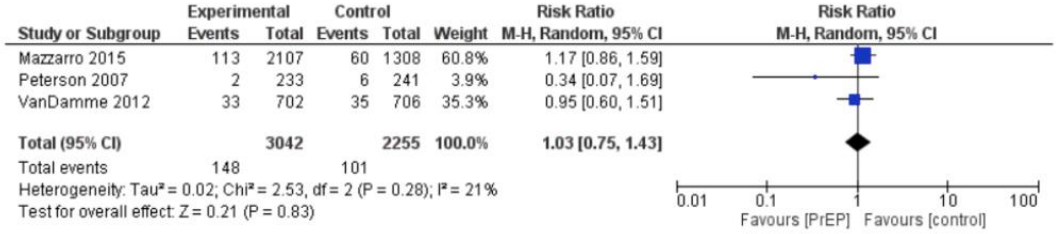


Figure S5. Meta-analysis: HIV acquisition in heterosexual participants, PrEP versus placebo, studies with low (<80%) adherence

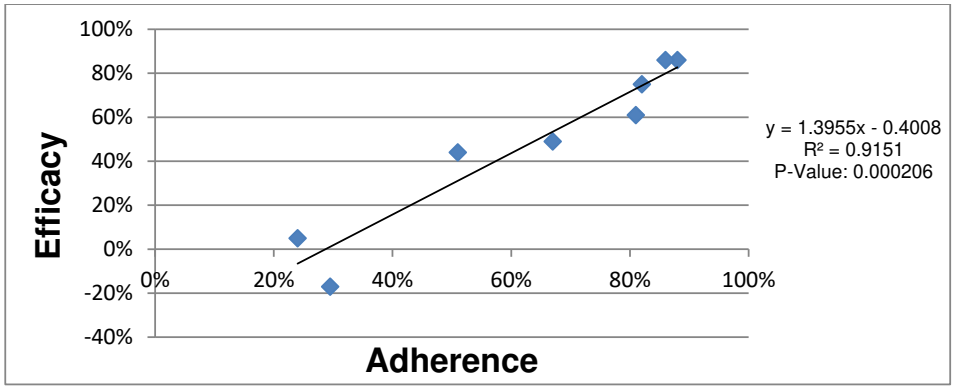


Supplementary Material

Adherence

Figure S3 compares efficacy and adherence (measured by plasma drug concentration of participants, or plasma drug confirmation of self-reported adherence; n=7 trials). A regression model yielded a R^2 of 0.92 ($p<0.001$).

Figure S6. Efficacy as a function of adherence



Caption: Only trials that reported plasma drug concentrations contributed to anlaysis: (Baeten 2012 (Partners PrEP), Choopanya 2013 (Bangkok Tenofovir Study), Grant 2010 (iPrEx), Mazzarro 2015 (VOICE), McCormack 2015 (PROUD), Molina 2015 (Ipergay), Thigpen 2012 (TDF2 study), VanDamme 2012 (FEM-PrEP)

Supplementary Material

Safety

Figure S7. Meta-analysis: 'any adverse event', PrEP versus placebo

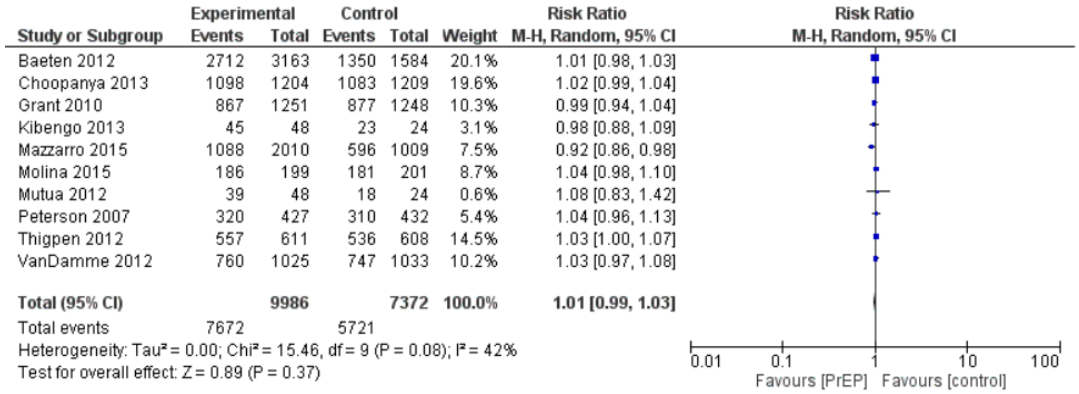


Figure S8. Meta-analysis: 'any adverse event', tenofovir/emtricitabine versus tenofovir

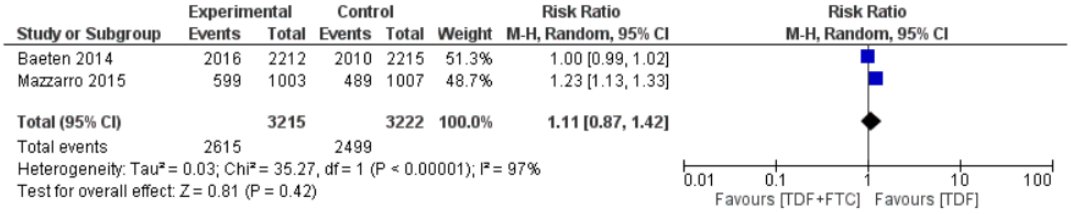
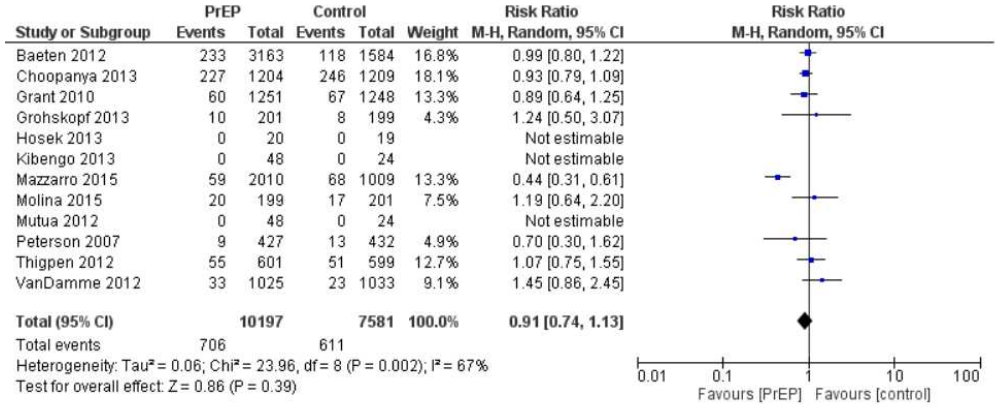
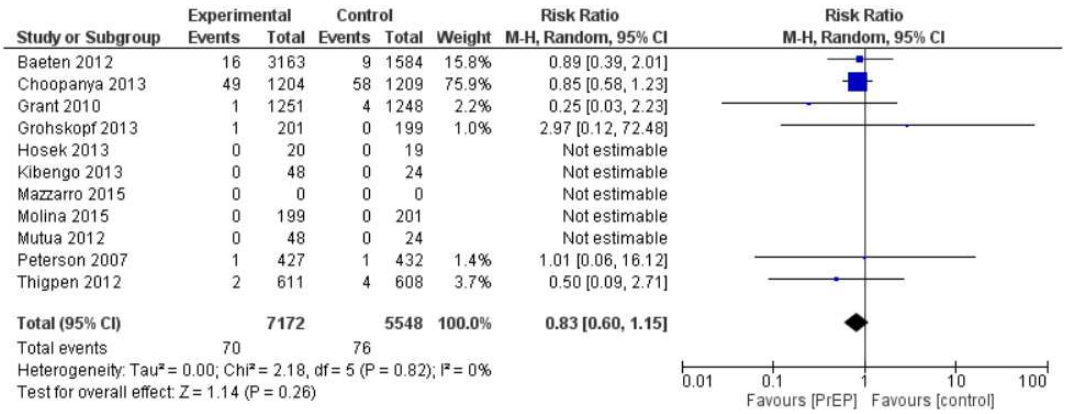


Figure S9. Meta-analysis: serious adverse events, PrEP versus placebo



Supplementary Material

Figure S10. Meta-analysis: deaths, PrEP versus placebo



Supplementary Material

Viral drug resistance mutations

Figure S11. Meta-analysis: any drug mutation (acute HIV at enrolment), PrEP versus placebo

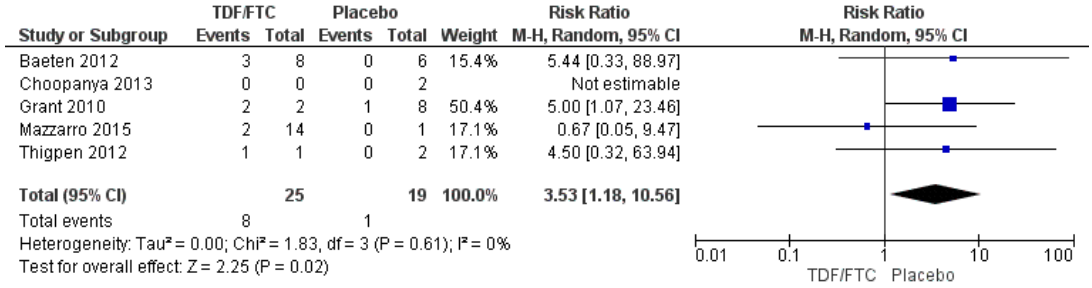
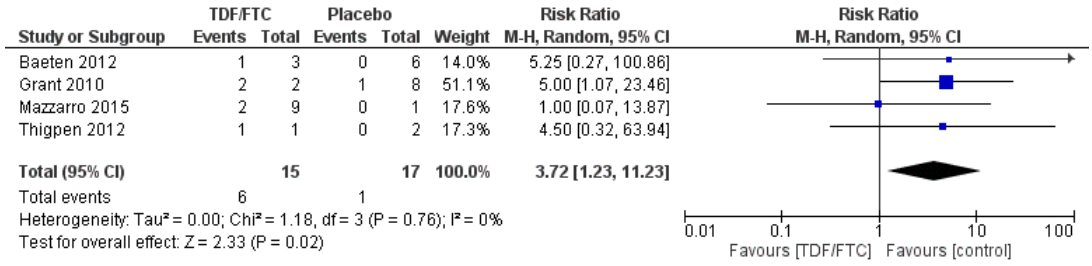


Figure S12. Meta-analysis: emtricitabine mutation (acute HIV at enrolment), tenofovir/emtricitabine versus placebo



Supplementary Material

S3.4

Results from Thigpen 2012 (by gender)

Number of HIV infections and PrEP efficacy by gender

	Tenofovir-emtricitabine group	Placebo group	Efficacy	95% CI	p-value
Female	7	14	49.4	-21.5, 80.8	0.11
Male	2	10	80.1	24.6, 96.9	0.03

Cohort is modified intention-to-treat; note that disaggregated data on overall number of male and female participants in each study arm not reported, precluding the evaluation of absolute risk.

S3.5 Adherence, as measured in primary studies

Study	Intervention	Adherence
Bekker 2018 (ADAPT Cape Town)	Tenofovir/emtricitabine (daily, time and event-driven PrEP)	• 75% (7,283 of 9,652 doses taken) for daily regimen; 65% (2,367 of 3,616 doses taken) for time-driven regimen and 53% (1,161 of 2,203 doses taken) for those event-driven regimen by electronic drug monitoring.
Baeten 2012 (Partners PrEP)	Tenofovir/emtricitabine and tenofovir (three arms: two active arms and one placebo arm)	• Factoring in missed visits, other reasons for non-dispensation of study medication and non-adherence to dispensed study pills, 92.1% of follow-up time was covered by study medication. • Among 29 subjects on the tenofovir and emtricitabine/tenofovir arms who acquired HIV-1, 31% had tenofovir detected in a plasma sample at the seroconversion visit compared with 82% of 902 samples from a randomly-selected subset of 198 subjects who did not acquire HIV-1.
Baeten 2014 (Partners PrEP)	Tenofovir/emtricitabine and tenofovir (two active arms)	• Study medication was taken by participants on 90.0% of days during follow-up time (factoring in protocol-defined study medication interruptions, missed visits, and non-adherence to dispensed study pills, as measured by monthly pill counts of returned study tablets). • Among subjects who acquired HIV-1, the minority (14/51, 27.5%) had tenofovir detected in a plasma sample at the visit at which HIV-1 seroconversion was detected, compared with the majority (1,047/1,334, 78.5%) of samples from a randomly selected subset of subjects who did not acquire HIV-1.
Choopanya 2013 (Bangkok Tenofovir Study)	Tenofovir (daily)	• Adherence was assessed daily at directly observed therapy (DOT) visits and monthly at non-DOT visits using a study drug diary. On the basis of participants' study drug diaries, participants took the study drug an average (mean) of 83.8% of days. • Plasma samples were obtained from 46 participants with incident HIV infections the day infection was detected, and from 282 HIV-negative participants to test for the presence of tenofovir. Tenofovir was detected in one (1%) of 177 participants in the placebo group and 100 (66%) of 151 participants in the tenofovir group. • In the case-control analysis in participants assigned to tenofovir, tenofovir was detected in the plasma of 5 (39%) of 13 HIV-positive participants and 93 (67%) of 138 HIV-negative participants.
Grant 2010 (iPrEx)	Tenofovir/emtricitabine (daily)	• The rate of self-reported pill use was lower in the emtricitabine–tenofovir group than in the placebo group at week 4 (mean, 89% vs. 92%) and at week 8 (mean, 93% vs. 94%) but was similar thereafter (mean, 95% in the two groups). • The percentage of pill bottles returned was 66% by 30 days and 86% by 60 days. • Among subjects in the emtricitabine–tenofovir group, at least one of the study-drug components was detected in 3 of 34 subjects with HIV infection (9%) and in 22 of 43 seronegative control subjects (51%).

Grohskopf 2013 (CDC Safety Study)	Tenofovir (daily)	• Adherence was measured by pill count, medication event monitoring system (MEMS) and self-report; adherence ranged from 77% (pill count) to 92% (MEMS).
Kibengo 2013 (IAVI Uganda Study)	Tenofovir/emtricitabine (daily or intermittent)	• Median MEMS adherence rates were 98% (IQR: 93–100) for daily PrEP regimen, 91% (IQR: 73–97) for fixed intermittent dosing and 45% (IQR: 20–63) for post-coital dosing. • There was no difference in adherence rates between active and placebo groups, thus these two groups were combined for the adherence analyses.
Hosek 2013 (Project PrEPare)	Tenofovir/emtricitabine (daily)	• Self-reported medication adherence averaged 62% (range 43–83%) while rates of detectable tenofovir in plasma of participants in the emtricitabine/tenofovir arm ranged from 63.2% (week 4) to 20% (week 24).
Mazzarro 2015 (VOICE)	Tenofovir (oral), tenofovir/emtricitabine (oral) and vaginal tenofovir gel (all daily)	• 90% by self-report, 86% by returned products and 88% as assessed with audio computer-assisted self-interviewing (ACASI). • In a random sample, tenofovir was detected in 30%, 29% and 25% of available plasma samples from participants randomly assigned to receive tenofovir, tenofovir/emtricitabine and tenofovir gel, respectively.
McCormack 2015 (PROUD)	Tenofovir/emtricitabine (daily)	• Overall, sufficient study drug was prescribed for 88% of the total follow-up time. • Tenofovir was detected in plasma of all 52 sampled participants (range 38–549 ng/mL) who reported that they were taking PrEP.
Molina 2015 (Ipergay)*	Tenofovir/emtricitabine (intermittent)	• Median pills per month: 15 pills. • In the tenofovir–emtricitabine group, the rates of detection were 86% for tenofovir and 82% for emtricitabine, respectively, a finding that was consistent with receipt of each drug within the previous week. Tenofovir and emtricitabine were also detected in eight participants in the placebo group, three of whom were receiving postexposure prophylaxis. • Computer-assisted structured interviews also performed to assess most recent sexual episode. Overall, 28% of participants did not take tenofovir-emtricitabine or placebo, 29% took the assigned drug at a suboptimal dose and 43% took the assigned drug correctly.
Mutua 2012 (IAVI Kenya Study)	Tenofovir/emtricitabine (daily or intermittent)	• There was no difference in adherence rates between treatment and placebo groups, thus these groups were combined for the adherence analyses. Median MEMS adherence rates were 83% (IQR: 63–92) for daily dosing and 55% (IQR:28–78) for fixed intermittent dosing (p=0.003).
Peterson 2007 (West Africa Study)	Tenofovir (daily)	• The amount of product used was estimated by subtracting the number of pills returned from the number dispensed, and dividing this number by the total number of days in the effectiveness analysis. • Drug was used no more than 69% of study days. Excluding time off product due to pregnancy, drug was used for no more than 74% of study days.

Thigpen 2012 (TENOFOVIR2)	Tenofovir/emtricitabine (daily)	• The two groups had similar rates of adherence to the study medication as estimated by means of pill counts (84.1% in the tenofovir–emtricitabine group and 83.7% in the placebo group, P = 0.79) and self-reported adherence for the preceding 3 days (94.4% and 94.1%, respectively; P = 0.32). • Among the four participants in the tenofovir–emtricitabine group who became infected with HIV during the study, two (50%) had detectable levels of tenofovir and emtricitabine in plasma obtained at the visit before and closest to their estimated seroconversion dates. Among a small sample who did not undergo seroconversion, 55 (80%) and 56 (81%) had detectable levels of tenofovir and emtricitabine, respectively.
VanDamme 2012 (FEM-PrEP)	Tenofovir/emtricitabine (daily)	• At the time of study-drug discontinuation, 95% of participants reported that they had usually or always taken the assigned drug. Pill-count data were consistent with ingestion of the study drug on 88% of the days on which it was available to the participants. • In contrast, drug-level testing revealed much lower levels of adherence. Among women with seroconversion in the tenofovir–emtricitabine group, the target plasma level of tenofovir was identified in 7 of 27 women (26%) at the beginning of the infection window (excluding six women for whom the window started at enrolment), in 7 of 33 (21%) at the end of the window, and in 4 of 27 (15%) at both visits. Among the uninfected control participants, the numbers of women with target-level tenofovir were somewhat higher: 27 of 78 women (35%) at the beginning of the infection window, 35 of 95 (37%) at the end of the window, and 19 of 78 (24%) at both visits.

Tenofovir = Tenofovir Disoproxil Fumarate

* non-daily regimen

S3.6 Change in sexual behaviour/STI rates

Study	Measure	Outcome
Baeten 2012 (Partners PrEP)	• Having sex without a condom with HIV-positive partners in prior month • STI diagnoses from sex acts outside partnership	• At enrolment, 27% of HIV-1 seronegative partners reported sex without condoms with their HIV-1 seropositive partner during the prior month. This percentage decreased during follow-up (to 13% and 9% at 12 and 24 months) and was similar across the study arms. • The proportion reporting outside partnerships and who acquired sexually transmitted infections during follow up did not differ across the study arms.
Baeten 2014 (Partners PrEP)	Unreported	
Bekker 2018 (ADAPT Cape Town)	Unreported	
Choopanya 2013 (Bangkok Tenofovir Study)	• Drug use behaviour • Number of sexual partners	• Tenofovir and placebo recipients reported similar rates of injecting and sharing needles and similar numbers of sexual partners during follow up with no interactions between time and treatment group. • Overall, number of participants reporting injecting drugs or sharing needles reduced over time. • Sex with more than one partner decreased from 522 (22%) at enrolment to 43 (6%) at month 72.
Grant 2010 (iPrEx)	• Number of anal sex acts • Proportion of anal sex acts with a condom • STI diagnoses	• Sexual practices were similar in the two groups at all time points. • The total numbers of sexual partners with whom the respondent had receptive anal intercourse decreased, and the percentage of those partners who used a condom increased after subjects enrolled in the study. • There were no significant between-group differences in the numbers of subjects with syphilis, gonorrhea, chlamydia, genital warts or genital ulcers during follow-up.
Grohskopf 2013 (CDC Safety Study)	Unreported	
Hosek 2013 (Project PrEPare)	Male-to-male unprotected anal sex acts	• No significant differences among the three treatment groups across visits. • Insignificant trend from baseline to week 24 of decreasing unprotected anal sex acts across all treatment arms.
Kibengo 2013 (IAVI Uganda Study)	HIV behaviour change	• The median number of sexual partners in the past month remained at 1 (IQR: 1–1) during the trial. • No other HIV risk behaviours reported at baseline changed during the trial
Mazzarro 2015 (VOICE)	Unreported	
McCormack 2015 (PROUD)	• Number of sexual partners • Incident STIs	• Total number of different anal sex partners varied widely between baseline and year 1. No significant difference between groups at one year was detected. • Proportion with confirmed rectal chlamydia/gonorrhea was similar in immediate and delayed arms (proxy for condomless anal intercourse). • Adjusted odds ratio for rectal chlamydia or gonorrhea: 1.00 (0.72–1.38) (adjusted for number of sexual health screens)

Molina 2015 (Ipergay)	• Total number of sexual intercourse events • Proportion of events without a condom • Number of sexual partners • Incident STIs	• Sexual practices did not change overall among the participants during the study period as compared with baseline: there were no significant between group differences in the total number of episodes of sexual intercourse in the four weeks before, in the proportion of episodes of receptive anal intercourse without condoms, or in the proportion of episodes of anal sex without condoms during the most recent sexual intercourse. • There was a slight but significant decrease in the number of sexual partners within the past two months in the placebo group as compared with the tenofovir—emtricitabine group (7.5 and 8, respectively; p = 0.001). • The proportions of participants with a new sexually transmitted infection (of the throat, anus, and urinary tract combined) during follow-up were similar, with 41% in the tenofovir—emtricitabine group and 33% in the placebo group (P = 0.10).
Mutua 2012 (IAVI Kenya Study)	HIV behaviour change	• The median number of sexual partners in the past month increased from three (IQR 2–4) at baseline to four (IQR 2–8) at month 4 during the trial. • Because there may have been underreporting of sex partners at baseline, authors also compared the median number of sexual partners month 2 (4) and at month 4 (4).
Peterson 2007 (West Africa Study)	• Condom use at last sex • Number of sex acts • Number of partners	• During screening, participants reported an average of 12 coital acts per week with an average of 21 sexual partners in the previous 30 days (including 11 new partners). During follow-up, participants reported an average of 15 coital acts per week, with an average of 14 sexual partners in the previous 30 days (six new partners). Of note, most participants in this study were sex workers. • Self-reported condom use increased from 52% at screening (average across all sites during the last coital act prior to screening) to approximately 92% at the enrolment, month 3, month 6, and month 9 visits, to 95% at the month 12 visit (for acts occurring during the last seven days). The average condom use during the follow-up period was 92%.
Thigpen 2012 (TENOFOVIR2)	• Protected sex episodes with main/ most recent casual partner • Number of sexual partners	• The percentage of sexual episodes in which condoms were used with the main or most recent casual sexual partner was similar in the two study groups at enrolment (81.4% [range, 76.6 to 86.4] in the tenofovir–emtricitabine group and 79.2% [range, 71.6 to 87.6] in the placebo group, P = 0.66) and remained stable over time. • The reported number of sexual partners declined in both groups during the course of the study.
VanDamme 2012 (FEM-PrEP)	• Number of partners • Sex acts without a condom • Pelvic STIs	• There was no evidence of increased HIV risk behaviour during the trial, with modest but significant reductions in the numbers of partners (mean reduction, 0.14; P<0.001 by paired-data t-test), vaginal sex acts (mean reduction, 0.58; P<0.001), and sex acts without a condom (mean reduction, 0.46; P<0.001) reported by women at the last follow-up visit, as compared with seven days before enrolment.

Supplementary Material

		• Fewer than half the study participants agreed to undergo a pelvic examination. There were no significant between-group differences in the prevalence of pelvic STIs.

O Murchu E, *et al*. *BMJ Open* 2022; 12:e048478. doi: 10.1136/bmjopen-2020-048478